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Feasibility of conducting a lung-cancer chemoprevention trial among tin miners in Yunnan, P. R. China

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Tin miners in Yunnan Province in southern China have an extremely high rate of lung cancer, more than one percent per year among those at 'high risk' (40+ years old, with 10+ years of underground mining and/or smelting experience). The extraordinary lung cancer rates result from combined exposure to radon, arsenic, and tobacco smoking (cigarettes and/or bamboo water pipe). A study to determine the feasibility of conducting a large-scale, lung-cancer chemoprevention trial was conducted in 1986 among currently employed or retired miners from the Yunnan Tin Corporation in the city of Gejiu. The study was designed to answer four questions: (i) Could potentially eligible miners be identified and recruited? (ii) Could intervention agents be shipped successfully from the United States to the study area and be appropriately distributed? (iii) Would miners adequately adhere to the study protocol and comply with the intervention regimen? (iv) Could potential adverse effects be monitored and documented? The six-month feasibility study yielded affirmative answers to each of these questions. A roster of over 7,000 high-risk miners was compiled. Four agents (vitamin A, 25,000 IU; β-carotene, 50 mg; vitamin E, 800 IU; and selenium, 400 μg) were administered daily with placebos to 350 miners according to a 2^4 factorial design. Adherence, assessed by pill counts and serum micronutrient levels, was approximately 90 percent. The findings from this preliminary study indicate that a full-scale, lung-cancer chemoprevention trial in this population is feasible.

Key words: Carcinogens, chemoprevention trial, China, micronutrients, miners, P.R. China.

Introduction

Lung cancer is the leading cause of death from malignant neoplasms in the United States and many countries around the world, with the incidence of and mortality from this disease still on the increase in most areas.[1] Although reductions in the prevalence of cigarette smoking promise a future decline in lung cancer rates, a number of other, specific lung carcinogens have been identified, including asbestos, radon and its decay products, arsenic, polycyclic hydrocarbons, and other compounds.[2] Persons with lifelong exposures to these carcinogens are at high risk of developing lung cancer, and remain so even when active exposure has

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ceased. Thus, avoidance of smoking and exposure to other lung carcinogens must be considered the primary preventive strategy for lung cancer.

Epidemiologic investigations have implicated several micronutrients in the etiology of human cancer,[3] and laboratory studies have shown that administration of certain chemical compounds can reduce tumorigenesis in animal model systems.[4] Therefore, the possibility of chemoprevention—the administration of micronutrients or synthetic compounds to human populations to reduce the incidence of certain cancers—is undeniably attractive. It could be an important adjunct preventive strategy for lung cancer, especially for those who already have been exposed or cannot avoid being exposed to lung carcinogens. At the present time, however, this possibility is untested. Large-scale chemoprevention trials in human populations constitute the only definitive way of evaluating the possibility.

Sample size requirements for cancer prevention trials are driven in large part by incidence rates: the greater the incidence of a given cancer, the smaller the population needed to demonstrate a statistically significant reduction in cancer incidence.[5] For this reason, investigators look for populations at high risk of cancer in which to carry out prevention trials. In addition, one would like the potential study population to be relatively stable and geographically circumscribed.

For a lung cancer study, the tin-mining population around the city of Gejiu in Yunnan Province in southern China provides just such a study population. In order to determine whether a lung cancer chemoprevention trial could be carried out, we conducted a feasibility study between June and December 1986.

The feasibility study was designed to answer four questions:

(i) Could miners at high risk of lung cancer who were potentially eligible for the intervention study be identified and recruited?
(ii) Could intervention agents be successfully shipped to the study area, stored appropriately, and consistently distributed to the miners?
(iii) Would miners adhere to the study protocol, particularly with respect to pill consumption?
(iv) Could potential adverse effects from the intervention agents be monitored?

At the time this feasibility study was planned, four of the most promising compounds for chemoprevention of lung cancer were: retinol (vitamin A), β-carotene, alpha-tocopherol (vitamin E), and selenium. In addition, each of these four agents had been established as being relatively non-toxic and available. It should be emphasized that the feasibility study was not intended to test the chemopreventive efficacy of the four agents selected, but only to determine whether a long-term trial using the four agents could be implemented.

Methods

The Yunnan tin mines

The study was carried out among miners actively employed by or retired from the Yunnan Tin Corporation (YTC), located in Yunnan Province in southern China. YTC is a large, nonferrous-metals industry, formed in 1883 and nationalized after the establishment of the People's Republic in 1949. It is involved principally in the production of tin from the mines around the city of Gejiu, in the southern portion of Yunnan Province, where tin mining dates back 2,000 years. The total number of employees at the YTC in 1984 was 48,733, including 15,255 male miners with underground mining experience and/or smelting experience.

The extremely high incidence of lung cancer among Yunnan miners first attracted attention in China in 1968. Gejiu was found to have the highest lung cancer mortality rate in men among 2,392 counties or cities in all of China in the nation-wide mortality survey conducted in 1973-75.[6] Between 1954 and 1986, 1,743 cases of lung cancer were reported, of which 1,595 were confirmed by histologic examination or X-ray. Virtually all of the cases reported since 1973 have been confirmed histologically or cytologically. Among male miners aged 15 and over who had underground exposure, the crude annual incidence rate for 1983-85 was 585/100,000. Table 1 presents age- and period-specific incidence rates for miners with and without underground experience. Among underground miners aged 60-64, for example, the annual incidence rate for 1981-85 was 2,264/100,000. (By comparison, the SEER rate for US males aged 60-64 in 1978-81 was 304/100,000.[7])

Recent case-control studies have identified radon, arsenic, and tobacco as key factors in the genesis of lung cancer in this population.[8-10] In addition to the substantial concentrations of radon and radon-decay products in the mines, oxides of arsenic, as well as tin and various other metals, are contained in the ores mined by Gejiu. Miners have been exposed to arsenic in mine air, and arsenic trioxide is a by-product of the smelting process. Moreover, episodes of widespread arsenic contamination of local food and water supplies occurred in 1968, 1970, and 1978. Most miners have smoked for many years with the water pipe; more recently, cigarettes have been the preferred form of

Table 1. Annual age-specific lung cancer incidence rates, per 100,000 population

Age group	Yunnan (1981-85)		SEER (1978-81)
	Underground HX	No underground HX	
40-44	24	12	24
45-49	271	8	60
50-54	556	74	126
55-59	961	145	202
60-64	2,072	275	304
>64	2,729	603	475

tobacco smoking. Miners smoked water pipes while working underground until 1983 when this practice was prohibited.

Institute of Labor Protection

The Institute of Labor Protection (ILP), an organizational component of YTC, was created in 1974 to monitor working conditions and coordinate health and welfare efforts on behalf of mine employees. Prior to 1949, tunnel ceilings were low, mechanical ventilation was virtually nonexistent, and miners often had to work while crawling on their stomachs. Many of the miners began work as children. Since 1949, several of the older mines and smelters have been closed, and child labor has been abolished. In addition, ventilation ducts have been installed, shafts have been enlarged, and a number of worker protection practices have been implemented.

The ILP, which maintains a complete registry of lung cancer cases among miners, was the principal contractor for this feasibility study. Virtually all YTC employees who developed lung cancer were diagnosed and treated at the YTC Hospital.

Study population

Miners who are at least 40 years old and have had at least 10 years of underground and/or smelting experience have been targeted as a group at especially high risk of lung cancer. Annual screening, including a chest X-ray and sputum cytology, has been carried out by ILP on these miners since 1975. In 1984, approximately 14,000 miners were screened, including all those in the high-risk group. Cytologic review is performed by trained cytologists from the YTC Hospital.

A roster of miners considered to be high risk in 1986 was compiled. This roster provided information on age, number of years of underground and/or smelting work, and (for active miners) work unit (current mine or smelter where miner was employed). To be eligible for the feasibility study, participants had to meet all of the criteria shown in the Appendix.

Intervention assignment

Eligible participants were randomly assigned to one of 16 treatment groups, according to a 2^4 factorial design. This design is presented in detail in Table 2. In a factorial design, it is possible in one study to examine the efficacy of more than one treatment (or factor).[11] In this case, for each intervention agent, one-half of the subjects received potentially active agents, while one-half received a placebo. The doses of the four agents used were as follows: retinol, 25,000 IU daily; β-carotene, 50 mg daily, vitamin E, 800 IU daily; selenium (selenized yeast), 400 μg (elemental Se) daily.

Table 2. Factorial design (2^4)

	Placebo	*A*	*B*	*AB*
Placebo	Placebo	A	B	AB
C	C	AC	BC	ABC
D	D	AD	BD	ABD
CD	CD	ACD	BCD	ABCD

A = retinol (vitamin A), 25,000 IU daily.
B = β-carotene, 50 mg daily.
C = α-tocopherol (vitamin E), 800 IU daily.
D = selenium, 400 μg daily.

Baseline examination

The baseline examination consisted of:

(i) administration of a standardized interview form, comprising general sociodemographic information, a semiquantitative food-frequency questionnaire, and a detailed occupational and tobacco smoking history;
(ii) general medical history;
(iii) physical examination;
(iv) chest X-ray;
(v) sputum specimen for cytology;
(vi) collection of hair and nail specimens;
(vii) collection of one 10 cm^3 blood specimen to obtain serum for HBsAg, SGPT, retinol, β-carotene, vitamin E, and selenium.

Selenium analyses were performed at the ILP shortly after specimen collection. Atomic absorption spectrophotometry was used for selenium analysis. Aliquots of serum for retinol, β-carotene, and vitamin E analysis were stored in Beijing until the end of the study at which time the pre- and post-intervention sera were run in pairs using HPLC.[12] Serum was stored at −80°C at the ILP. Aliquots of serum also were sent in plastic containers on dry ice to the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) in Beijing where they were stored at −80°C.

Pill distribution

Both active agents and placebos were delivered in red soft-gelatin capsules. Each participant received four bottles, each containing 31 capsules, at baseline and at the beginning of each subsequent month. Participants were instructed to take one pill from each bottle every day. Bottles were labeled so that participants were unaware of the identity of the pill taken. Pill distributors were instructed to collect all bottles and unconsumed pills at the time of distribution of new bottles. All unconsumed pills were counted.

Serum micronutrient levels were determined for each of the intervention agents at baseline and at the follow-up examination. These were used as a biochemical assessment of adherence to the protocol. *T*-tests were used to compare the differences (treatment *cf* placebo group) of the differences (pre- *cf* post-intervention).

Monitoring of adverse effects

For the first month of the study, questionnaires were administered to each of the miners on a weekly basis to assess general health status as well as symptoms of possible toxicity from the four intervention agents. After the first month, the questionnaires were administered monthly. Symptoms were reported by the pill distributors to the field supervisor (a physician), who was responsible for further medical evaluation. In addition, miners could report symptoms directly to the local YTC health station, which then would contact the field supervisor.

Follow-up examination

In addition to the monthly symptom ascertainment and pill counts, participants had another blood specimen drawn at the end of the study. This specimen was shipped and stored in a manner similar to that of the baseline program.

Results

The study was carried out between 1 July 1986 and 24 December 1986. The four questions initially posed were answered as follows.

Question 1: Identification and recruitment of high-risk miners

A total of 6,379 miners were identified as being at high risk in 1986. Of these, 3,349 were currently employed, and the remainder were retired.

From the roster of high-risk miners, NCI investigators selected a random sample of 360 for entry into the feasibility study. This number was arbitrary, but reflected the investigators' estimate that a minimum of 300 participants was necessary to evaluate potential logistical difficulties. The results of efforts by Chinese investigators to contact and recruit these 360 miners are indicated in Table 3. A total of 167 subjects were recruited from the roster of high-risk miners to replace those from the original random sample who were unwilling or unable to participate.

At baseline examination, two of the 360 subjects were found to have lung cancer and were excluded from the intervention study. The number of subjects

Table 3. Results of initial recruitment efforts

Status	Number	Percent
Willing to participate	193	53.6
Unwilling or unable to participate	167	46.4
Taking vitamins	3	0.8
Serious illness	8	2.2
Lung cancer	9	2.5
Dead	19	5.3
Could not be located	59	16.4
Refused	69	19.2

who began taking the intervention agents was thus 358. Baseline characteristics of these 358 subjects are shown in Table 4. The number of participants assigned to each of the treatment groups is shown in Table 5.

A sample (21 percent) of interviews was repeated by the study supervisor. The information recorded by the study supervisor was found to correspond closely to that recorded by the original interviewers.

Question 2: Shipping, storage, distribution of intervention agents

The active agents and placebos were successfully shipped to the ILP from the US via Beijing and Kunming, the capital of Yunnan. The agents were kept for the duration of the study in locked cabinets in a storage room at the ILP.

Twenty-nine full-time and 39 part-time pill distributors were employed. These were trained in mid-May 1986 at the ILP. At that time, the rationale, overall study design, and specific pill distribution protocol were explained to the distributors. In addition, further instructions were given at the time of an NCI site-visit in June-July 1986, at the time of the baseline examination. The majority of study subjects lived in the vicinity of the mines or in the immediate Gejiu vicinity. Forty-eight (13.4 percent) of the subjects, however, lived outside the immediate Gejiu area, necessitating extensive travel to deliver the agents.

Table 4. Baseline characteristics of study subjects (July, 1986)

Characteristics	No.	
Median age	358	54 years
Median height	358	162 cm (5'4")
Median weight	358	56 kg (123 lb)
Median duration of underground experience	358	25.5 years
65 + years old	358	12%
Retired	358	43%
Ever been to school	358	62%
Ever smoked tobacco	356	93%
Ever smoked cigarettes	358	83%
Ever smoked waterpipe	356	76%
Mean serum retinol	336	57.0 μg/dl
Mean serum β-carotene	336	14.8 μg/dl
Mean serum vitamin E	336	848 μg/dl
Mean serum selenium	312	0.478 μg/ml

Table 5. Number of participants in each micronutrient treatment group[a]

Treatment	Treatment	Placebo
Vitamin A	180 (55.3)	178 (54.5)
β-carotene	179 (55.8)	179 (54.1)
Vitamin E	176 (54.6)	182 (55.2)
Selenium	180 (54.6)	178 (55.2)

[a]Mean ages (in years) are in parentheses.

Question 3: Adherence to protocol

A total of nine participants dropped out before the completion of the study. Four of these left the study in the first month because of chronic illness unrelated to the administration of the agents. Three left within the first month because of acute illnesses that may possibly have been related to an agent (one with an allergic dermatitis, the other two with continued gastric pain). Two subjects suffered fatal strokes in the fourth month. One of these was 55 years old and received vitamin E and selenium; the other was 53 years old and received placebo only.

Follow-up examinations, consisting of physical examinations and collection of blood specimens, were carried out between 16 December and 24 December 1988 on 337 subjects (94.1 percent). The 21 subjects who did not receive the follow-up examinations were out of the area at that time.

Pill counts were completed at the final visit. Because this final visit took place for some participants as much as several weeks after the scheduled study termination date (186 days after the baseline exam), participants could have continued to consume pills past the study termination date up to the final visit. It was assumed, therefore, in order to obtain the minimum (and most conservative) estimate of adherence, that pill counts reflected continued pill-taking up until the time of the final pill pick-up. The minimum adherence was calculated to be 85 percent for each of the agents.

Both pre- and post-intervention serum micronutrient data were available on about three-quarters of the participants. Table 6 presents mean pre- and post-intervention serum levels for each of the micronutrients according to treatment status. For β-carotene, vitamin E, and selenium, the micronutrient serum-level values increased substantially in both the treated and untreated groups, but the increase was much larger in the treated groups ($P < 0.0001$) for each micronutrient. For vitamin A, there were relatively smaller increases in the serum levels in the treated and untreated groups, but again the increase was substantially greater in the treated group ($P = 0.0004$).

Question 4: Monitoring adverse effects

Table 7 displays the frequency of certain symptoms specific to states of nutritional excess for the micronutrients administered. The data are presented for

Table 6. Mean pre- and post-intervention serum micronutrient levels by treatment status

Micronutrient	Untreated			Treated			*P*-value[a]
	No.[b]	Pre-	Post-	No.[b]	Pre-	Post-	
Vitamin A (μg/dl)	127	56.4	61.2	131	57.8	69.1	0.0004
β-carotene (μg/dl)	125	15.7	28.9	133	14.7	190	<0.0001
Vitamin E (μg/dl)	129	848	1,247	129	870	2,265	<0.0001
Selenium (μg/ml)	122	0.0485	0.0961	116	0.0479	0.437	<0.0001

[a]The *P*-values listed are derived from *t*-tests of the comparisons of the pre- to post-intervention differences for the untreated group vs the pre- to post-intervention differences for the treated group (the differences of the differences).
[b]The number of miners who had both pre- and post-intervention micronutrient values.

Table 7. Frequency[a] of symptoms reported,[b] pre- and post-intervention

Symptoms	Pre-intervention			Post-intervention		
	Often	Occasionally	Rarely	Often	Occasionally	Rarely
Muscle cramps	5	35	59	1	9	90
Diarrhea	5	38	57	0	10	90
Poor appetite	6	35	60	1	16	83
Runny nose	17	42	41	3	23	74
Joint pain	23	43	34	5	36	59
Joint pain (vitamin A only)	26	43	31	5	39	55
Chapping of lips/face	2	23	75	0	6	93
Chapping of lips/face (vitamin A only)	2	23	74	1	6	94
Yellowing of skin	1	10	89	0	1	99
Yellowing of skin (β-carotene only)	1	11	88	0	1	99
Broken nails	9	24	67	1	11	88
Broken nails (selenium only)	9	20	71	1	11	88
Hair loss	3	16	81	0	6	94
Hair loss (vitamin A only)	3	17	79	0	6	94
Tingling in limbs	2	10	88	1	2	97
Tingling in limbs (selenium only)	2	10	88	1	2	97
Headache	17	53	30	4	29	68
Headache (vitamin A only)	19	48	33	6	23	70
Lethargy	3	25	72	0	2	98
Lethargy (vitamin A only)	2	29	69	0	3	97
Lethargy (selenium only)	3	21	77	0	2	98

[a]Figures sometimes do not total 100% due to rounding.
[b]'Often' here includes "daily" and "often" from the questionnaire; 'rarely' here includes "rarely" and "never" from the questionnaire. Percentages are of all participants actually receiving one or more of the micronutrients, unless a specific micronutrient is indicated in parentheses, in which case the percentages are of only those receiving that micronutrient.

those who actually were treated with the pertinent micronutrient. Symptoms were reported generally to improve. For example, the frequency of broken nails (a symptom of toxicity) among those treated with selenium declined, as did the frequency of reported skin-yellowing among those taking β-carotene.

Discussion

For a number of years, the Institute of Labor Protection maintained a roster of high-risk miners—defined as those at least 40 years of age with at least 10 years of experience in underground mining and/or smelting. This roster comprises over 7,000 active and retired employees of the YTC. We also have learned that the Gejiu municipal mines, recently incorporated into YTC, had identified some 1,394 miners who would be eligible for the trial on the basis of the 40+ years old/10+ years of experience criteria. Moreover, the pool of potentially eligible miners could be expanded if the minimum number of years of experience in underground mining and/or smelting were reduced to, say, eight years, though the overall incidence rate in the study population then might decline somewhat. We are currently examining lung-cancer incidence rates by duration of underground/smelting experience to determine if sample size requirements for the study would be better met by reducing the required number of years of work experience.

Only about 54 percent of the 360 high-risk miners who were initially identified by NCI were willing and able to participate in the study. Of the initial sample, 16.4 percent could not be located, and 19.2 percent were unwilling to participate. This was of some concern, since the population of high-risk miners is certainly very large but is nevertheless finite. The Chinese investigators ascertained, however, that most of the 59 miners who could not be located had left the area for seasonal farming. Moreover, on the basis of a telephone survey carried out by the Anti-Cancer Office of the YTC, the majority of these indicated they would have been willing to participate in the study. The 69 miners who were unwilling to participate in the study apparently were concerned about possible side effects of the intervention agents. The Chinese investigators have estimated that most of these refusing subjects would be willing to participate in the larger trial if no serious side effects were seen in the feasibility study.

The loss to follow-up due to illness or death was minimal, 6/358 = 1.7 percent, though this figure would undoubtedly increase in a five-year trial. Over 94 percent of the study population received the follow-up examination.

The reporting and diagnosis of lung cancer in this population appear to be accurate and complete. A sample of 39 sputum-specimen slides that Chinese pathologists had identified previously as indicating lung cancer was reviewed by an NCI pathologist. The NCI pathologist confirmed 100 percent of the diagnoses.

Despite the fact that nearly half of the study participants were retired and some lived a considerable distance from the ILP, the pills were delivered successfully. We conclude, however, that greater emphasis needs to be placed on collection of pill bottles and unconsumed pills at the time of delivery of the next month's supply in order to get a more accurate pill count.

The use of serum micronutrient analyses was helpful in confirming that the treatment groups indeed did take the assigned intervention agents. Baseline serum selenium levels were very low in this population, with a mean level among the miners of only 0.0478 μg/ml (compared with a reported mean value of 0.136 in the US[13]). β-carotene levels were also low in this population (mean value of 14.8 μg/dl among study participants, compared with 22.5 μg/dl reported in the US.[14] The mean retinol and vitamin E levels for the miners at the baseline examination were comparable to values reported in the US; mean values for the miners were 57.0 μg/dl and 848 μg/dl, respectively, for these two nutrients, compared with average of 70.1 μg/dl[14] and 1,050 μg/dl[15] for US populations. The explanation for the small increases in these micronutrients in the untreated group is unclear, but might reflect some inconsistency in laboratory methods or dietary changes during the course of the study.

The increase in retinol levels in the group that received retinol was unexpected, since the retinol level is under rather tight homeostatic control in the body. The explanation may be storage, since the baseline bloods were stored for several months and analyzed at the same time as the follow-up specimens. The fact that the treatment group showed a greater increase in retinol than the untreated group might indicate some retinol deficiency in this population.

The capacity of the Chinese investigators to monitor potential adverse effects was demonstrated. The pill distributors were able to administer a questionnaire about symptoms to the participants on a regular basis. Three participants reported symptoms which were considered by the study supervisor, in consultation with a study physician, to be possible adverse effects of the intervention agents. (On further evaluation, the physician determined that only one of these participants could be considered to have had an allergic reaction to the agents.) These three participants stopped taking the agents immediately after this decision was made. The major complaint of participants was that the size of the pills made them difficult to swallow, but this abated as the study progressed. The reporting of improvement for a wide variety of symptoms likely reflects a placebo effect. The absence of any serious adverse effects, as well as the remarkable improvement in subjective health status, should be helpful in alleviating the fears of some potential participants who might otherwise have been unwilling to participate in the upcoming trial.

In summary, each of the four questions bearing on the feasibility of a lung-cancer chemoprevention trial was answered affirmatively. We conclude that a lung-cancer chemoprevention trial in this population is feasible. The future trial would likely involve several thousand study participants taking multiple intervention agents for at least five years. Newer agents, including synthetic retinoids and dithiolthiones, currently are being considered. It is likely that a full-scale trial will be preceded by a smaller study among the Yunnan miners to determine the effect of the proposed agents on an intermediate marker such as bronchial metaplasia.[16]

References

1. US Department of Health and Human Services, Public Health Service, National Institutes of Health. *1987 Annual Cancer Statistics Review*. Bethesda, MD: National Cancer Institute, 1988; NIH Pub. No. 88-2789.
2. Fraumeni JF, Blot WJ. Lung and pleura. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*. Philadelphia: WB Saunders Company, 1982: 564-82.
3. Zaridze DG. Diet and cancer. *Wld Rev Nutr Diet* 1986; **48:** 195-221.
4. Boone CW, Kelloff GJ, Malone WE. Identification of candidate cancer chemopreventive agents and their evaluation in animal models and human clinical trials: a review. *Cancer Res* 1990; **50:** 2-9.
5. Byar DP. Some statistical considerations for design of cancer prevention trials. *Preventive Medicine* 1989; **18:** 688-99.
6. Li J-Y, Liu B, Li G, *et al*, eds. *Atlas of Cancer Mortality in the People's Republic of China*. Shanghai: China Map Press, 1979.
7. Horm JW, Asire AJ, Young JL, Pollack ES. *SEER Program: Cancer Incidence and Mortality in the United States 1973-81*. Bethesda: US Dept Health and Human Services, Public Health Service, 1984; NIH Pub. No. 85-1837.
8. Qiao Y-L, Taylor PR, Yao S-X, *et al.* The relation of radon exposure to and tobacco use to lung cancer among tin miners in Yunnan Province, China. *Am J Ind Med* 1989; **16:** 511-21.
9. Taylor PR, Qiao, Y-L, Schatzkin A, *et al.* The relation of arsenic exposure to lung cancer among tin miners in Yunnan Province, China. *Brit J Ind Med* 1989; **129:** 395-406.
10. Lubin JH, Qiao Y-L, Taylor PR, Yao S-X, Schatzkin A, Mao B-I. Quantitative evaluation of the radon and lung cancer association in a case-control study of Chinese tin miners. *Cancer Res* 1990; **50:** 174-80.
11. Byar DP, Piantodosi S. Factorial designs for randomized clinical trials. *Can Treat Rep* 1985; **69:** 1055-62.
12. Miller KW, Yang CS. An isocratic high-performance liquid chromatography method for the simultaneous analysis of plasma retinol, alpha-tocopherol, and various carotenoids. *Anal Biochem* 1985; **145:** 21-6.
13. Willett WC, Polk BF, Morris JS, *et al.* Prediagnostic serum selenium and risk of cancer. *Lancet* 1983; **2:** 130-4.
14. Nirenberg DW, Stukel TA, Baron JA, *et al.* Determinants of plasma levels of beta-carotene and retinol. *Am J Epidemiol* 1989; **130:** 511-21.
15. Menkes MS, Comstock GW, Vuilleumier JP, Helsing KJ, Rider AA, Brookmeyer R. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *New Engl J Med* 1986; **315:** 1250-4.
16. Gouveia J, Hercend T, Lemaigre G, *et al.* Degree of bronchial metaplasia in heavy smokers and its regression after treatment with a retinoid. *Lancet* 1982; **i:** 710-2.

Appendix

Eligibility criteria

1. At least 40 years of age.
2. At least a total of 10 years of underground mining experience and/or smelting experience.
3. Neither suspicious nor positive cytology.
4. Chest radiograph not suspicious for cancer.
5. No serious illness that would interfere with adherence to the protocol or would likely cause death within a five-year period.
6. SGPT 40, or 40-60, as long as hepatomegaly and HBsAg not both present. Miners with SGPT >60 were automatically excluded.
7. Taking no vitamin or mineral supplements (including, *e.g.*, retinoids or selenium preparations).
8. Taking no medications, like anticoagulants, that may interact with one or more of the nutritional intervention agents.
9. Have given written, informed consent.
10. Willing and able to participate.